Madrigal Pharmaceuticals Highlights Presentations at The Liver Meeting Digital Experience™, The American Association for the Study of Liver Diseases Meeting November 13, 2020, Including NASH Expert Insights on the Ongoing Open Label Arm of Resmetirom 52-W

November 13, 2020

- *Dr. Stephen Harrison will present Resmetirom for the Treatment of NASH: Early Data from the Phase 3 MAESTRO Clinical Trials | The Liver Meeting Digital Experience™, AASLD Product Theater on Friday, November 13, 2020, at 4:30 PM ET.*

- *In the 100 mg open label arm of MAESTRO-NAFLD:*
  - *At week 16, MRI-PDFF (magnetic resonance imaging-proton density fat fraction) reduction compared to baseline was 53% overall (p<0.0001) and up to 62% in key subgroups*
  - *At weeks 12-24, statistically significant lowering of liver enzymes, inflammatory biomarkers and atherogenic lipids and lipoproteins were observed*
  - *At week 16, compared to baseline, a meaningful reduction (p=0.003) in magnetic resonance elastography (MRE), a measure of liver of fibrosis and inflammation was seen*

CONSHOHOCKEN, Pa., Nov. 13, 2020 (GLOBE NEWSWIRE) -- Madrigal Pharmaceuticals, Inc. (NASDAQ:MDGL), announced that Dr. Stephen Harrison, M.D., Medical Director for Pinnacle Clinical Research, San Antonio, Texas, and Visiting Professor of Hepatology, Oxford University, and Principal Investigator of the MAESTRO studies, will make an oral presentation today at 4:30 PM ET at The Liver Meeting Digital Experience™,The American Association for the Study of Liver Diseases Meeting, November 2020 accessible via the Product Theaters and Satellite Symposium page. Dr. Harrison's presentation, based on data from studies with MGL-3196 (resmetirom), will also highlight key insights from three posters, which are available to registered attendees on The Liver Meeting Digital Experience™ website throughout the four-day meeting. Resmetirom is the first orally administered, small-molecule, liver-directed, truly β-selective thyroid hormone receptor (THR) agonist and is currently in Phase 3 development for the treatment of NASH patients both with biopsy-confirmed fibrosis stage 2-3 (ClinicalTrials.gov NCT03900429) and in presumed NASH subjects diagnosed non-invasively (ClinicalTrials.gov/NCT04197479).

Dr. Harrison commented, "In the MAESTRO- NASH study, using a series of readily available tests such as FibroScan, MRI-PDFF and PRO-C3 in patients with metabolic risk factors (diabetes, obesity, dyslipidemia and hypertension) we have demonstrated that, in recruiting a clinical trial, NASH with advanced fibrosis (F2-F3) may be confirmed on liver biopsy with an increasing level of confidence. The MAESTRO-NAFLD-1 study in patients with presumed NASH diagnosed non-invasively, now with 1,200 enrolled patients, is helping to build a robust safety and efficacy data set in NASH patients treated with resmetirom."

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, stated, "Interim data from the ongoing open label arm of MAESTRO-NAFLD-1 confirm the safety and efficacy at a 100 mg dose of resmetirom, with 80% of patients achieving at least a 30% reduction from baseline in liver fat measured on MRI-PDFF, and more than half achieving a 50% or greater reduction in liver fat at Week 16, both of which percentage fat reductions have been associated with increased NASH resolution and reduction in liver fibrosis on subsequent liver biopsy in resmetirom treated patients. The reduction in MRE at Week 16 is novel, and consistent with potential fibrosis and inflammation reductions in patients with baseline F1-F3 fibrosis. MRE is potentially a more accurate measurement of liver fibrosis than other non-invasive measures such as FibroScan because MRE measures a larger area of the liver, and may demonstrate correlations with Week 52 liver biopsy in MAESTRO-NASH. Of note, no safety flags have been observed at the 100 mg dose in the open-label arm, consistent with earlier Phase 1 and Phase 2 data."

Paul Friedman, M.D., Madrigal's Chief Executive Officer, added, "The open label arm of MAESTRO-NAFLD-1 provides opportunities to observe safety and the potential benefits of resmetirom treatment on an ongoing basis in non-cirrhotic NASH and compensated NASH cirrhotic patients, with completion of the double-blind arms of the study in the next 12 months. We believe that these data will inform the results of the blinded 80 and 100 mg arms of the MAESTRO-NAFLD-1 and MAESTRO-NASH studies."

POSTER PRESENTATIONS

- **#1657 ALGORITHM FOR PREDICTING ADVANCED NASH FIBROSIS ON SCREENING BIOPSY IN RESMETIROM PHASE 3 MAESTRO-NASH CLINICAL TRIAL**
  Dr. Stephen A Harrison[1], Dr. Rebecca A. Taub[2], Prof. Morten Asser Karsdal[3], John Franc[2], Dr. Mustafa R Bashir[4], Mr. Jordan Mark Barbone[2], Dr. Guy Neff[5], Dr. Nadege T Gunn[1] and Dr. Sam Moussa[6], (1) Pinnacle Clinical Research, (2) Madrigal Pharmaceuticals, (3) Biomarkers & Research, Nordic Bioscience, (4) Department of Radiology, Duke University Medical Center, (5) Covenant Research, LLC, (6) Medical, Adobe Gastroenterology

  MAESTRO-NASH is a Phase 3 double-blind placebo-controlled serial liver biopsy study to evaluate resmetirom for the treatment of NASH with F2 or F3 fibrosis and an exploratory F1 arm. Data was assessed for the power of the screening

paradigm to predict eligible NASH with fibrosis on liver biopsy. These data suggest that PRO-C3 is a marker not only of fibrosis stage in NASH but also of the level of NASH activity (inflammation and ballooning) in the NASH liver. In the absence of a liver biopsy, elevated PRO-C3 in the setting of metabolic syndrome (or FIBC3 (PRO-C3 [age, BMI, platelets, T2D]), fibroscan and MRI-PDFF may predict advanced NASH.

- **#1707 TREATMENT WITH RESMETIROM IN PHASE 3 MAESTRO-NAFLD-1 NASH STUDY OPEN LABEL ARM: EFFECTS ON BIOMARKERS AND IMAGING**
  Dr. Stephen A Harrison, Pinnacle Clinical Research, Dr. Naim Alkhouri, Arizona Liver Health, Dr. Rebecca A. Taub, Madrigal Pharmaceuticals, Dr. Guy Neff, Covenant Research, LLC, Dr. Seth J Baum, Excel Medical Clinical Trials and Dr. Mustafa R Bashir, Department of Radiology, Duke University Medical Center Data from the ongoing Open Label Arm of Madrigal's MAESTRO-NAFLD-1 trial will be presented.

  In this 52-week Phase 3 open label study, NASH patients identified using non-invasive imaging and biomarkers were treated with resmetirom 100 mg and demonstrated rapid reduction in hepatic fat, biomarkers and atherogenic lipids after 12-16 weeks of treatment, potentially supporting use of non-invasive tests to monitor individual NASH patient response to resmetirom treatment.

	All	**SHBG (high)**
MRI-PDFF (%)		
Baseline (%)	17.6	17.9
Relative % Change	-53%	-62%
p-value	<0.0001	<0.0001
MRE (kPa)		
Baseline (>2.9, F1-F3)	3.5	3.5
Absolute Change	-0.34	-0.46
p-value	0.003	0.003

- **#1675 IMPROVEMENT OF HEALTH-RELATED QUALITY OF LIFE IS ASSOCIATED WITH IMPROVEMENT OF FAT FRACTION BY MRI-PDFF IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS TREATED WITH RESMETIROM**
  Dr. Zobair M. Younossi, MD, MPH, FAASLD[1], Maria Stepanova[2], Dr. Rebecca A. Taub[3], Mr. Jordan Mark Barbone[3], Dr. Sam Moussa[4]and Dr. Stephen A Harrison[5], (1) Center for Liver Disease, Department of Medicine, Inova Health System, (2) Center for Outcomes Research in Liver Diseases, Washington, DC, United States, (3) Madrigal Pharmaceuticals, (4) Medical, Adobe Gastroenterology, (5) Pinnacle Clinical Research

  A review of patient reported outcome data from resmetirom's Phase 2 NASH study demonstrates that NASH patients treated with resmetirom who had liver fat reduction also improved some quality of life measures, particularly physical components such as bodily pain. Ongoing Phase 3 studies will assess long-term sustainability of quality of life improvements with resmetirom treatment.

About Resmetirom (MGL-3196)
Thyroid hormone, through activation of its β-receptor in hepatocytes, plays a central role in liver function impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver. Thyroid hormone receptor (THR)-β action in the liver is key to proper function of the liver, including regulation of mitochondrial activity such as breakdown of liver fat and control of the level of normal, healthy mitochondria. Patients with NASH have reduced levels of thyroid hormone activity in the liver with resultant impaired hepatic function, in part due to the inflamed state of the liver that causes degradation of thyroid hormone.

To exploit the thyroid hormone receptor (THR)-β pathway for therapeutic purposes in cardio-metabolic and liver diseases, it is important to avoid activity at the THR-α receptor, the predominant systemic receptor for thyroid hormone that is responsible for activity outside the liver including in heart and bone. The lack of selectivity of older thyromimetic compounds, chemically-related toxicities and undesirable distribution in the body led to safety concerns. Madrigal recognized that greater selectivity for thyroid hormone receptor (THR)-β and liver targeting might overcome these challenges and deliver the full therapeutic potential of THR-β agonism. Resmetirom has been shown to be highly selective based on 1) THR-β receptor functional selectivity based on both in vitro and in vivo assays and 2) specific uptake into the liver, its site of action, virtually avoiding any uptake into tissues outside the liver. In short and long term human and animal studies, resmetirom has been confirmed to be safe and devoid of activity at the THR-α receptor and without impact on bone or cardiac parameters. Resmetirom does not impact the thyroid axis hormones, including the central thyroid axis. Madrigal believes that resmetirom is the first orally administered, small-molecule, liver-directed, truly β-selective THR agonist.

About the Phase 3 Registration Program for the Treatment of NASH (Non-alcoholic steatohepatitis)
Analyses from the resmetirom Phase 2 NASH study demonstrate that the magnitude of liver fat reduction accurately predicts NASH resolution and liver fibrosis reduction and, specifically, that the resmetirom doses being used in Madrigal's Phase 3

MAESTRO-NASH trial could achieve the level of fat reduction predictive of NASH resolution and fibrosis reduction [Madrigal COVID and ABSTRACT Press Release_20200414].

The Phase 3 MAESTRO-NASH trial is expected to enroll 900 patients with biopsy-proven NASH (fibrosis stage 2 or 3), randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. After 52 weeks of treatment a second biopsy is performed. The primary surrogate endpoint on biopsy will be NASH resolution, with at least a 2-point reduction in NAS (NASH Activity Score), and with no worsening of fibrosis. Two key secondary endpoints are liver fibrosis improvement of at least one stage, with no worsening of NASH, and lowering of LDL-cholesterol [ClinicalTrials.gov/NCT03900429].

A second 52-week Phase 3 multi-center, double-blind, randomized, placebo-controlled study of resmetirom, MAESTRO-NAFLD-1, was initiated in December 2019 in 700 patients with non-alcoholic fatty liver disease (NAFLD), presumed NASH, randomized 1:1:1 to receive resmetirom 80 mg once a day, 100 mg once a day, or placebo. MAESTRO-NAFLD-1 also includes a 100 mg resmetirom open label arm in more than 100 non-cirrhotic NASH patients and additional open-label patients with compensated NASH cirrhosis. The trial was expanded to include more than 1,200 patients, in order to significantly enhance resmetirom's safety database and provide further opportunity to study selected patient subgroups. Unlike MAESTRO-NASH, MAESTRO-NAFLD-1 is a non-biopsy study and represents a "real-life" NASH study. NASH or presumed NASH is documented using historical liver biopsy or non-invasive techniques including FibroScan and MRI-PDFF. Using non-invasive measures, MAESTRO-NAFLD-1 is designed to provide incremental safety information to support the NASH indication as well as provide additional data regarding clinically relevant key secondary efficacy endpoints to better characterize the potential clinical benefits of resmetirom on cardiovascular and liver related endpoints. These key secondary endpoints include LDL-cholesterol, apolipoprotein B and triglyceride (TG) lowering; reduction of liver fat as determined by magnetic resonance imaging, proton density fat fraction (MRI-PDFF); and reduction of PRO-C3, a NASH fibrosis biomarker. [ClinicalTrials.gov/NCT04197479] Additional secondary and exploratory endpoints will be assessed including reduction in liver enzymes, FibroScan scores and other fibrosis and inflammatory biomarkers.

These and other data, including safety parameters, form the basis for potential subpart H submission to FDA for accelerated approval for the treatment of NASH. The original 900 patients in the MAESTRO-NASH study will continue on therapy after the initial 52-week treatment period; up to another 1,100 patients are to be added using the same randomization plan and the study is expected to continue for up to 54 months to accrue and measure clinical events, most relevantly progression to cirrhosis.

About Resmetirom's Potential to Confer Cardiovascular Risk Reduction in NASH patients
Additionally, resmetirom lowers multiple atherogenic lipids, including LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein (a), as demonstrated in Phase 2, a key differentiating factor compared with other NASH therapeutics. The magnitude of reduction of these lipids support a potential indication for treatment of hyperlipidemia in NASH patients and predicts a potential for benefit on cardiovascular (CV) events in NASH patients who die most frequently of CV, not liver disease.

Because of their diabetes, dyslipidemia, hypertension, obesity in concert with an inflamed, fatty liver, NASH patients, particularly those with advanced fibrosis, are at a substantially increased CV risk compared to the general population. Resmetirom's ability to decrease liver fat, which is an independent risk factor for CV events, and resmetirom's effect to reduce atherogenic lipids are being further evaluated in several key secondary endpoints in both MAESTRO Phase 3 clinical studies.

About Madrigal Pharmaceuticals
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics that target a specific thyroid hormone receptor pathway in the liver, which is a key regulatory mechanism common to a spectrum of cardio-metabolic and fatty liver diseases with high unmet medical need. Madrigal's lead candidate, resmetirom, is a first-in-class, orally administered, small-molecule, liver-directed, thyroid hormone receptor (THR)-β selective agonist that is in currently in two Phase 3 clinical studies, MAESTRO-NASH and MAESTRO-NAGLD-1, designed to demonstrate multiple benefits across a broad spectrum of NASH (non-alcoholic steatohepatitis) and NAFLD (non-alcoholic fatty liver disease) patients. For more information, visit www.madrigalpharma.com.

Forward-Looking Statements
This communication contains "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on our beliefs and assumptions and on information currently available to us, but are subject to factors beyond our control. Forward-looking statements include but are not limited to statements or references concerning: our clinical trials; research and development activities; the timing and results associated with the future development of our lead product candidate, MGL-3196 (resmetirom); our primary and secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment or biomarker effects with resmetirom; the predictive power of liver fat reduction on NASH resolution with fibrosis reduction or improvement; the achievement of enrollment objectives concerning patient number, safety database and/or timing for our studies; the predictive power of liver fibrosis reduction with resmetirom using non-invasive tests, including the use of MRE; the predictive power of non-invasive tests generally, including for purposes of recruiting a NASH clinical trial; potential NASH or NAFLD patient risk profile benefits with resmetirom; and our possible or assumed future results of operations and expenses, business strategies and plans, capital needs and financing plans, trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things. Forward-looking statements: reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; and can be identified by terms such as "allow," "anticipates," "be," "believes," "continue," "could," "demonstrates," "design," "estimates," "expects," "forecasts," "future," "goal," "hopeful," "inform," "intends," "may," "might," "plans," "potential," "predicts," "predictive," "projects," "seeks," "should," "will," "would"

or similar expressions and the negatives of those terms. Although management presently believes that the expectations reflected in such forward-looking statements are reasonable, it can give no assurance that such expectations will prove to be correct and you should be aware that actual results could differ materially from those contained in the forward-looking statements.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: our clinical development of resmetirom; enrollment uncertainties, generally and in relation to COVID-19 shelter-in-place and social distancing measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that includes substantially more patients than our prior studies; the timing and outcomes of clinical studies of resmetirom; and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward- looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the occurrence of unanticipated events. Please refer to Madrigal's filings with the U.S. Securities and Exchange Commission for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied. We specifically discuss these risks and uncertainties in greater detail in the section entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2019 and our Quarterly Report on Form 10-Q for the period ended June 30, 2020, as well as in our other filings with the SEC.

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